

FIGURE 1

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NO. 123 P. 7

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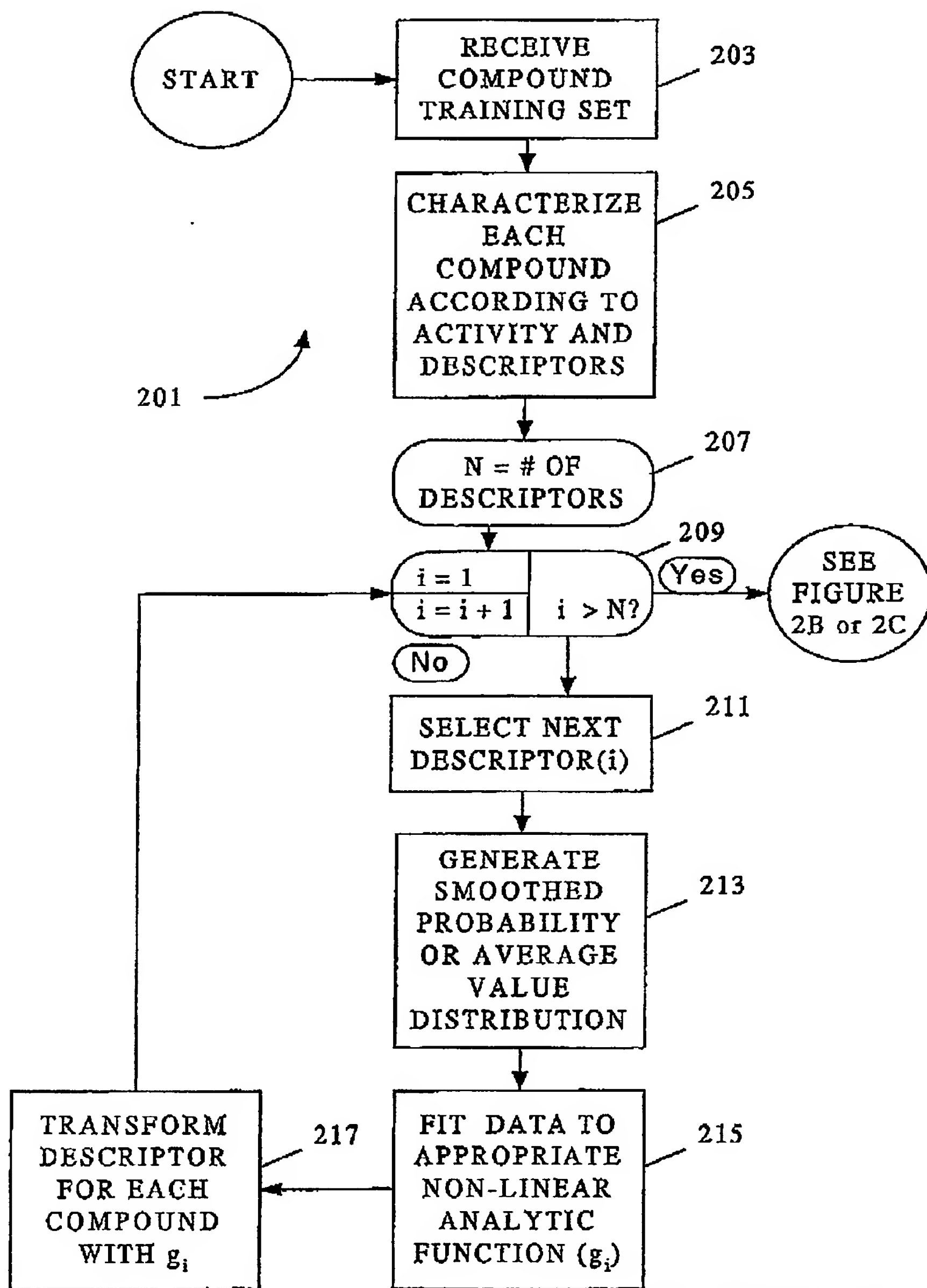


FIGURE 2A

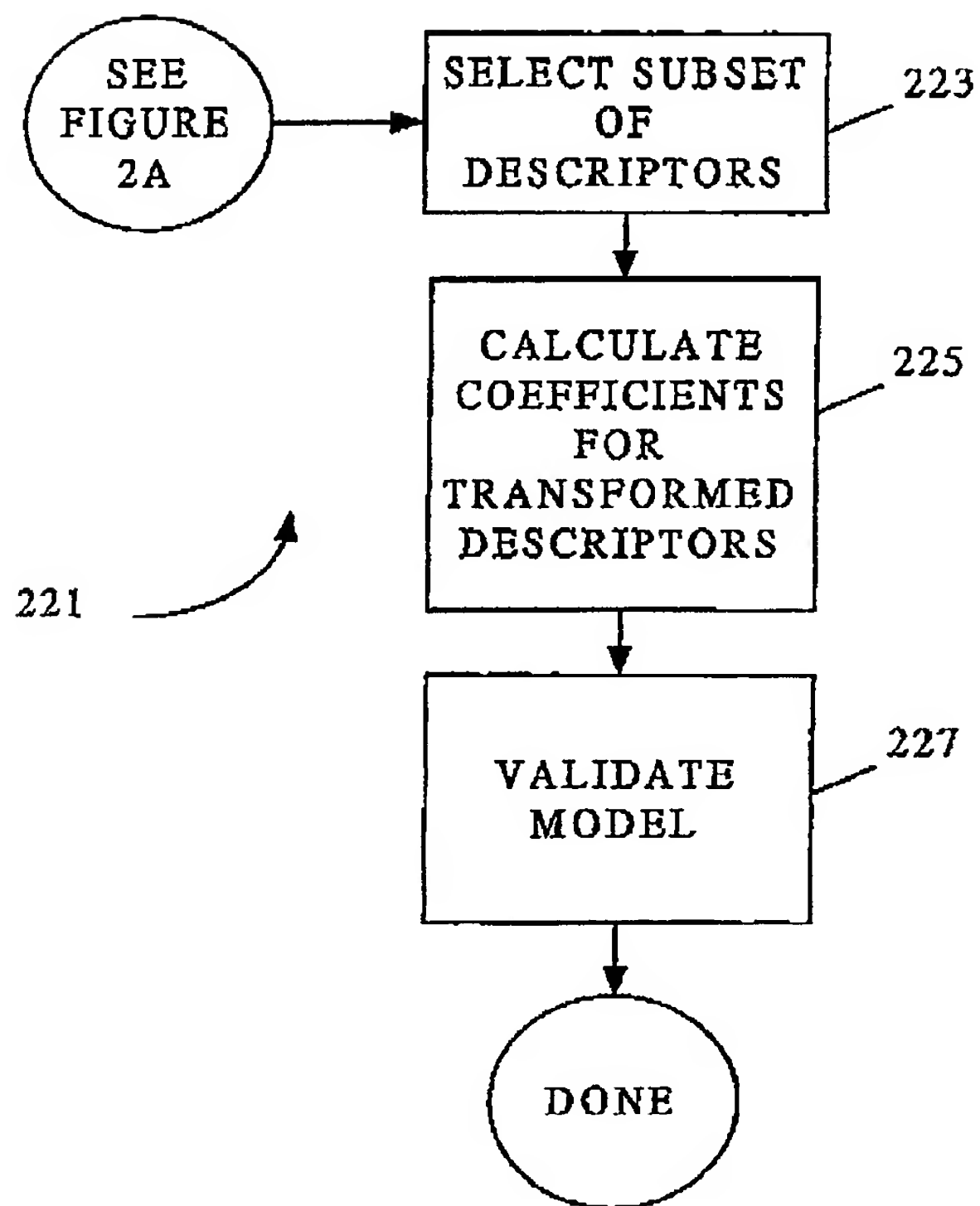


FIGURE 2B

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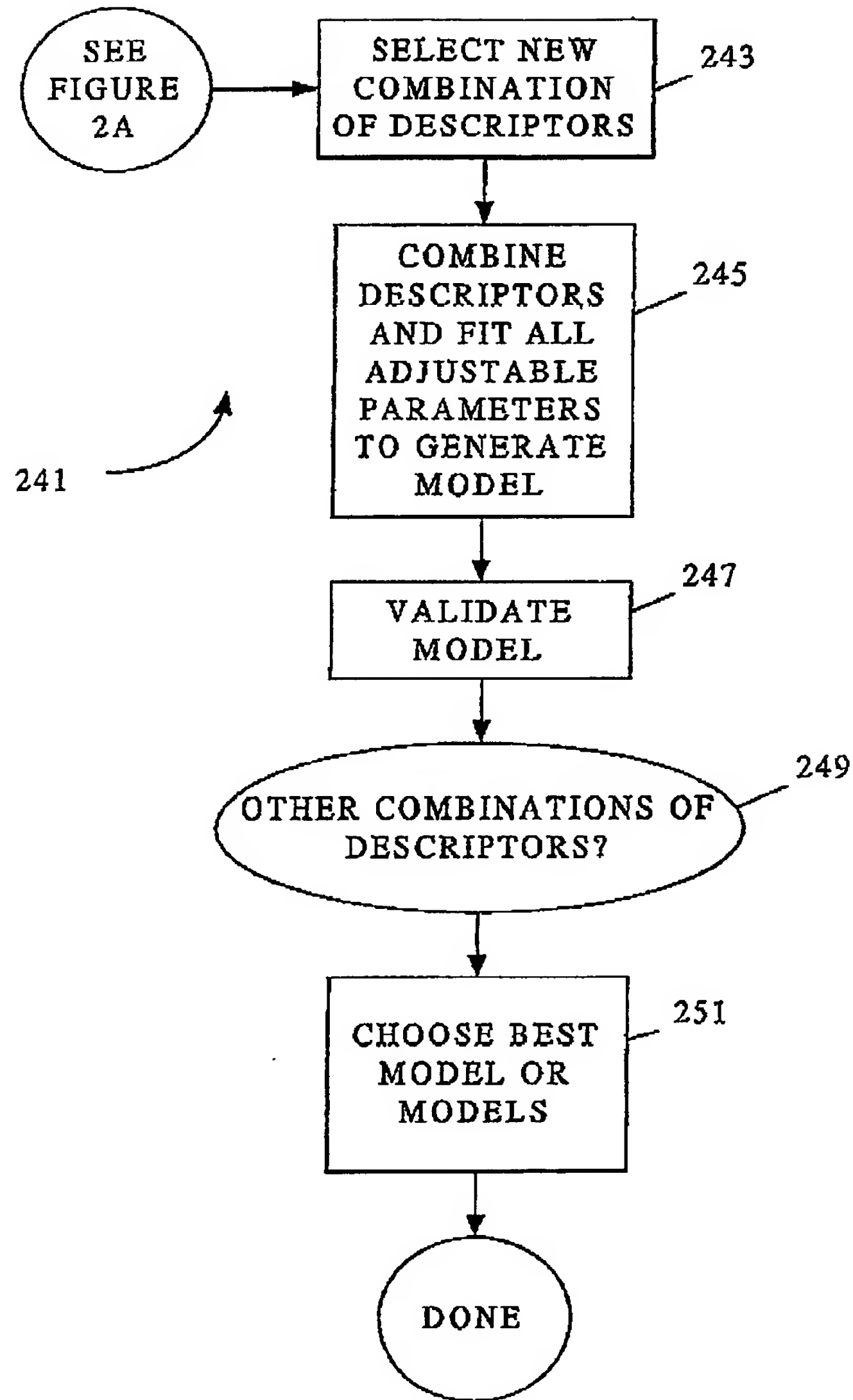


FIGURE 2C

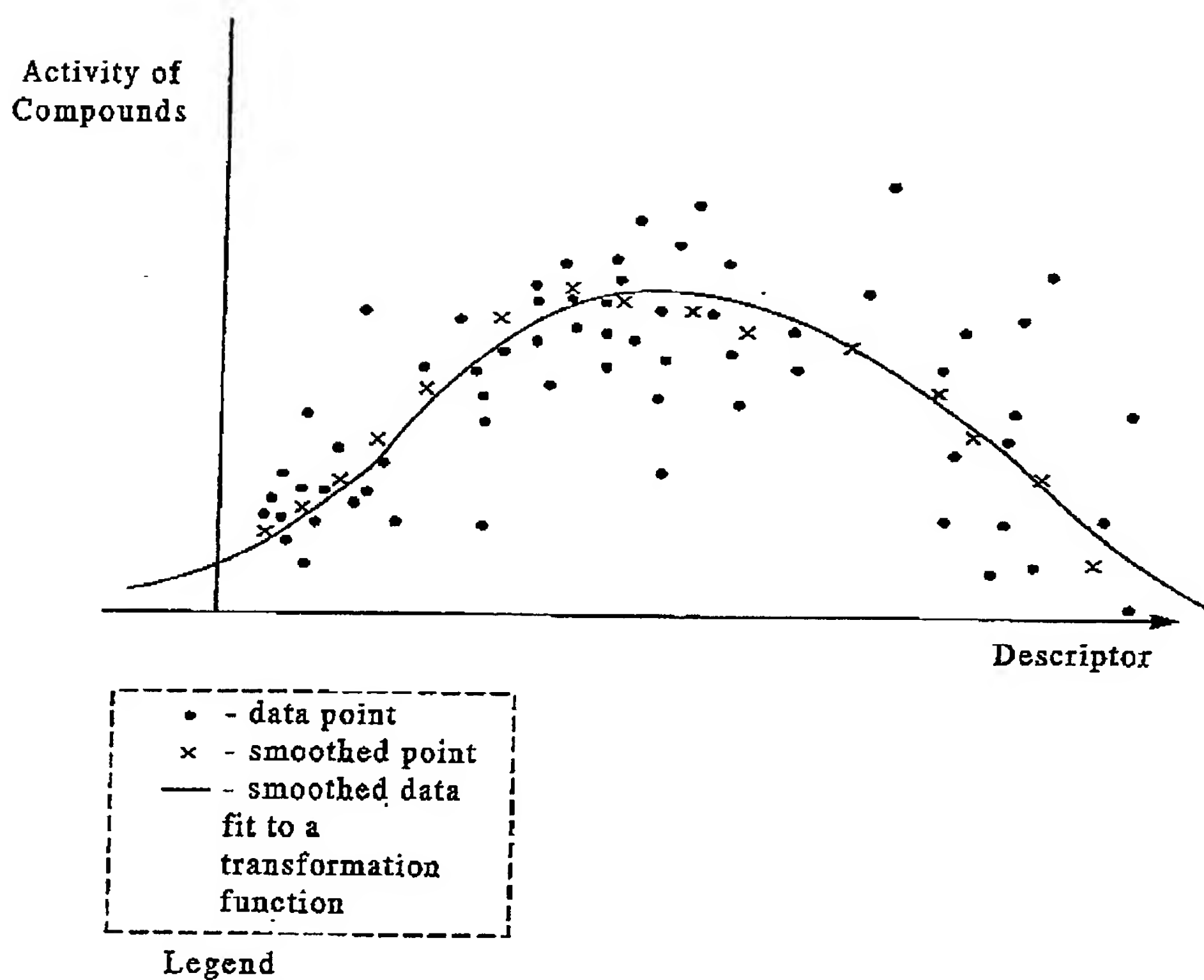
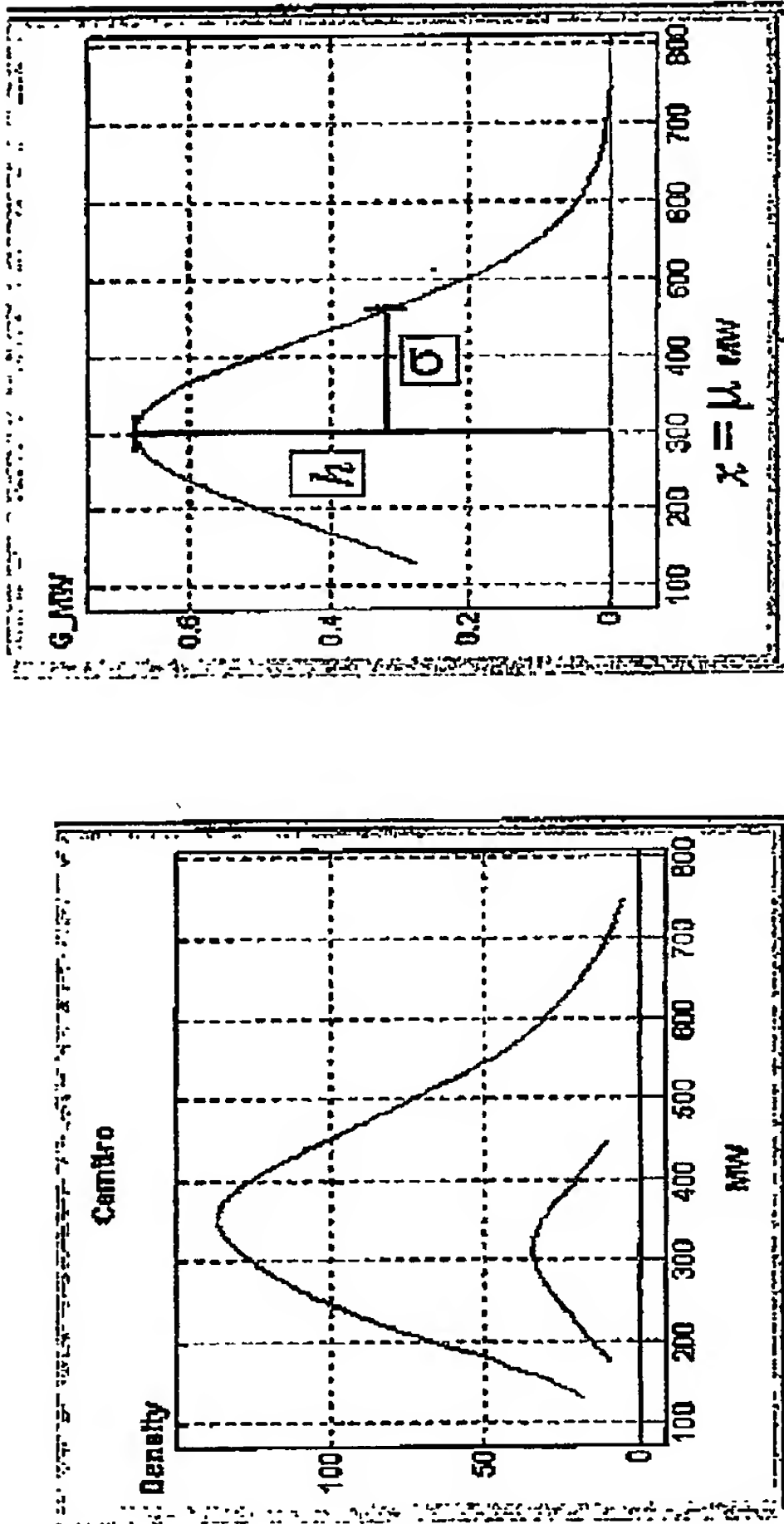


FIGURE 3

Optimum Molecular Weight



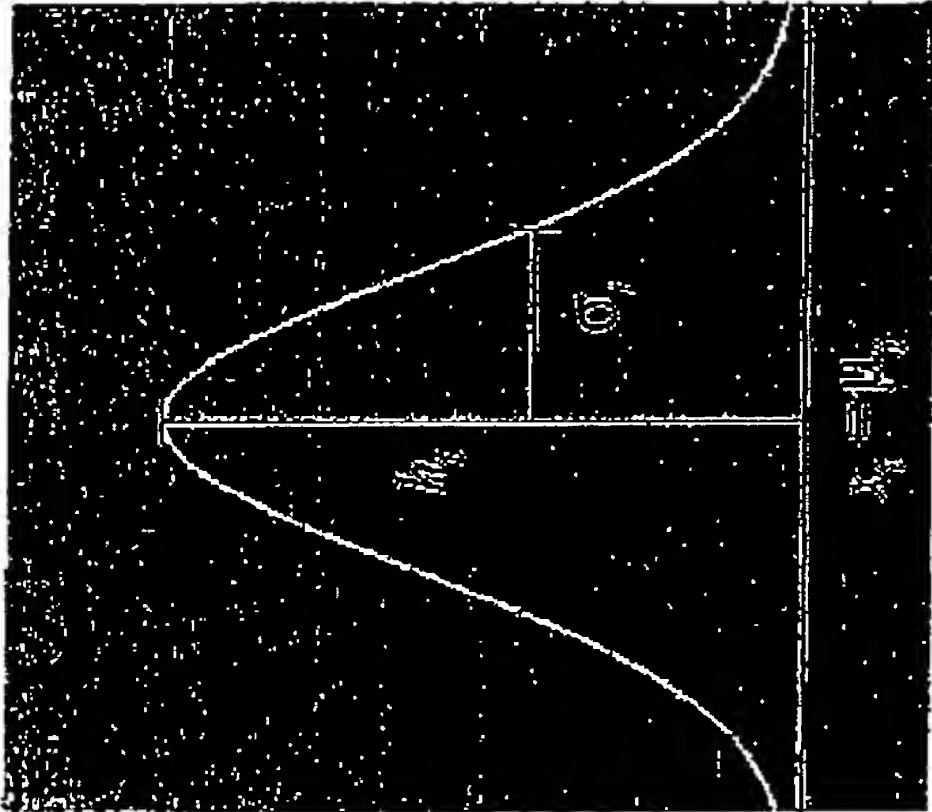
$$g(x) = h e^{-\frac{(x-\mu)^2}{4\sigma^2}}$$

FIGURE 4A

N-Dimensional Gaussian Modeling

Additive

$$g(x_{i..N}) = \frac{1}{N} \sum_{i=1}^N h_i e^{-\frac{(x_i - \mu_i)^2}{4\sigma_i^2}}$$



Multiplicative

$$g(x_{i..N}) = h e^{-\frac{1}{N} \sum_{i=1}^N (x_i - \mu_i)^2 / 4\sigma_i^2}$$

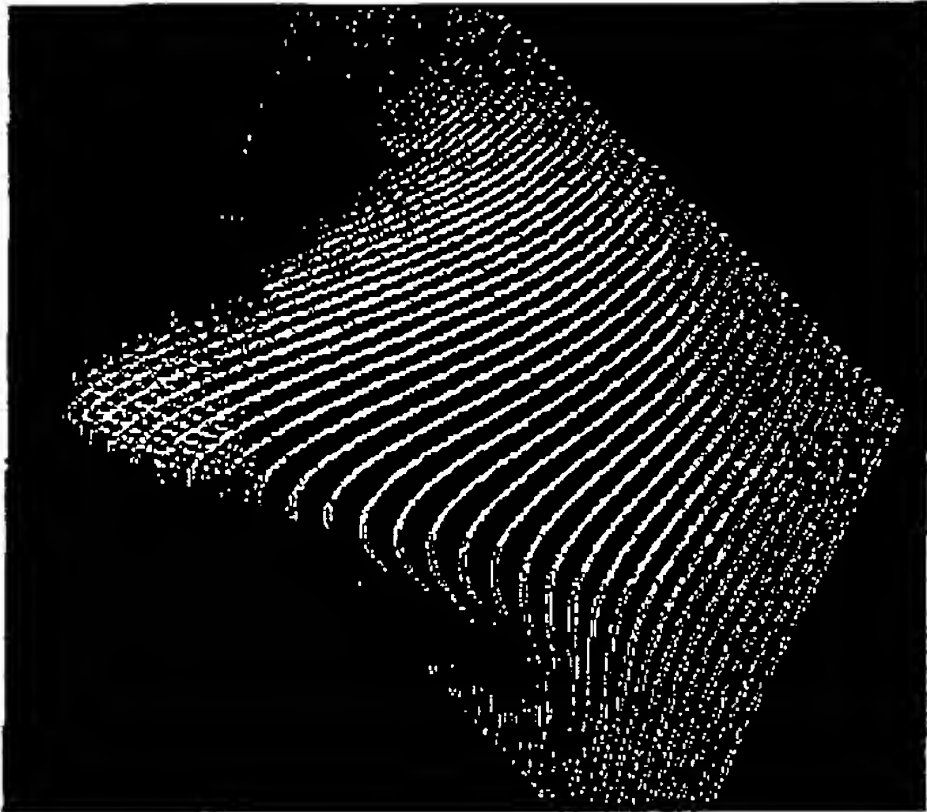


FIGURE 4B

Optimization Function

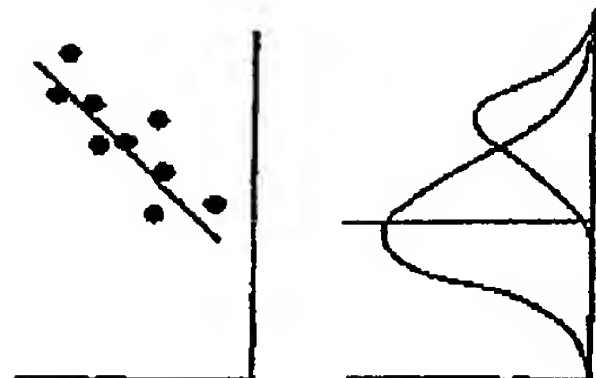
$$g(X, \mu, \sigma, h, t) = t + he^{-\sum_{k=1}^{N_x} (x_k - \mu_k)^2 / 4\sigma_k^2}$$

$$f = S_{inh} \left[\frac{1}{N_{inh}} \sum_{i=1}^{N_{inh}} (g(X_i, \mu, \sigma, h, t) - y_i)^2 \right] \text{ Mean of the Squared Errors of Inhibitor Affinity}$$

$$+ S_{drug} \left[\frac{1}{N_{drug}} \sum_{j=1}^{N_{drug}} (g(X_j, \mu, \sigma, h, t) - \bar{y}_{drug})^2 \right] \text{ Squared Error of the Means of Drug Affinity}$$

$$+ S_{fit} \left[\sigma_y^2 \sum_{k=1}^{N_x} \left(\frac{\mu_k - \mu_{qk}}{\text{range}(X_k^T)} \right)^2 + (t - t_0)^2 \right] \text{ Constraints to prevent Overfitting}$$

FIGURE 4C



Initial Values for Optimization

$$t_0 = \min(y)$$

$$h_0 = \max(y) - t_0$$

$$\mu_{0,k} = \frac{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2 x_{k,i}}{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2}$$

$$\sigma_{0,k} = \sqrt{\frac{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2 (x_{k,i} - \mu_k)^2}{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2}}$$

$$\sigma_y = \sqrt{\frac{\sum_{i=1}^{N_{inh}} (y_i - \bar{y}_{inh})^2}{N_{inh} - 1}}$$

FIGURE 4D

Gaussian Optimization Function

$$f(\mathbf{x}) = t + h e^{-\sum_{k=1}^{N_x} (x_k - c_k)^2 / 4w_k^2}$$

$$f_o = s_y \left(\frac{\sum_{i=1}^{N_y} u_i (f(\mathbf{x}_i) - y_i)^2}{\sigma_y^2 \sum_{i=1}^{N_y} u_i} \right) + s_c \sum_{k=1}^{N_x} \frac{(c_k - c_{0,k})^2}{\sigma_{x_k}^2} + s_w \sum_{k=1}^{N_x} \frac{\sigma_{x_k}}{w_k} + s_t \frac{(t - t_0)^2}{\sigma_y^2}$$

Weighted Mean Squared Error

Center Constraint

Width (Focus) Constraint

Tare Constraint

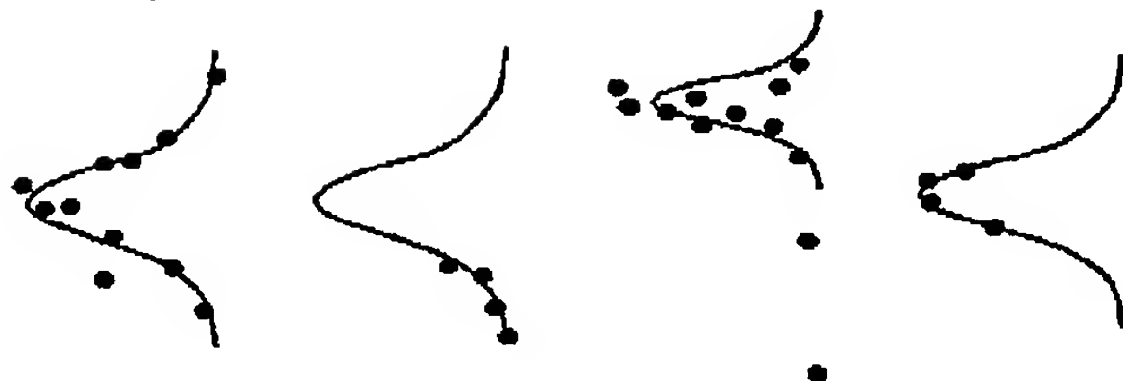


FIGURE 4E

Performance Metrics

$n_k = \frac{\sigma_{x_k}}{w_k}$	<p>Descriptor Focus</p>
$s = \sqrt{\frac{\sum_{i=1}^{N_y} u_i (f(\mathbf{x}_i) - y_i)^2}{\sum_{i=1}^{N_y} u_i}}$	<p>Standard Error</p>
$r^2 = \frac{\left(\sum_{i=1}^{N_y} u_i (f(\mathbf{x}_i) - \bar{f}(\mathbf{x})) (y_i - \bar{y}) \right)^2}{\sum_{i=1}^{N_y} u_i (f(\mathbf{x}_i) - \bar{f}(\mathbf{x}))^2 \sum_{i=1}^{N_y} u_i (y_i - \bar{y})^2}$	<p>Correlation Coefficient</p>
$q^2 = 1 - s^2 / \sigma_y^2$	<p>Residual Error</p>

FIGURE 4G

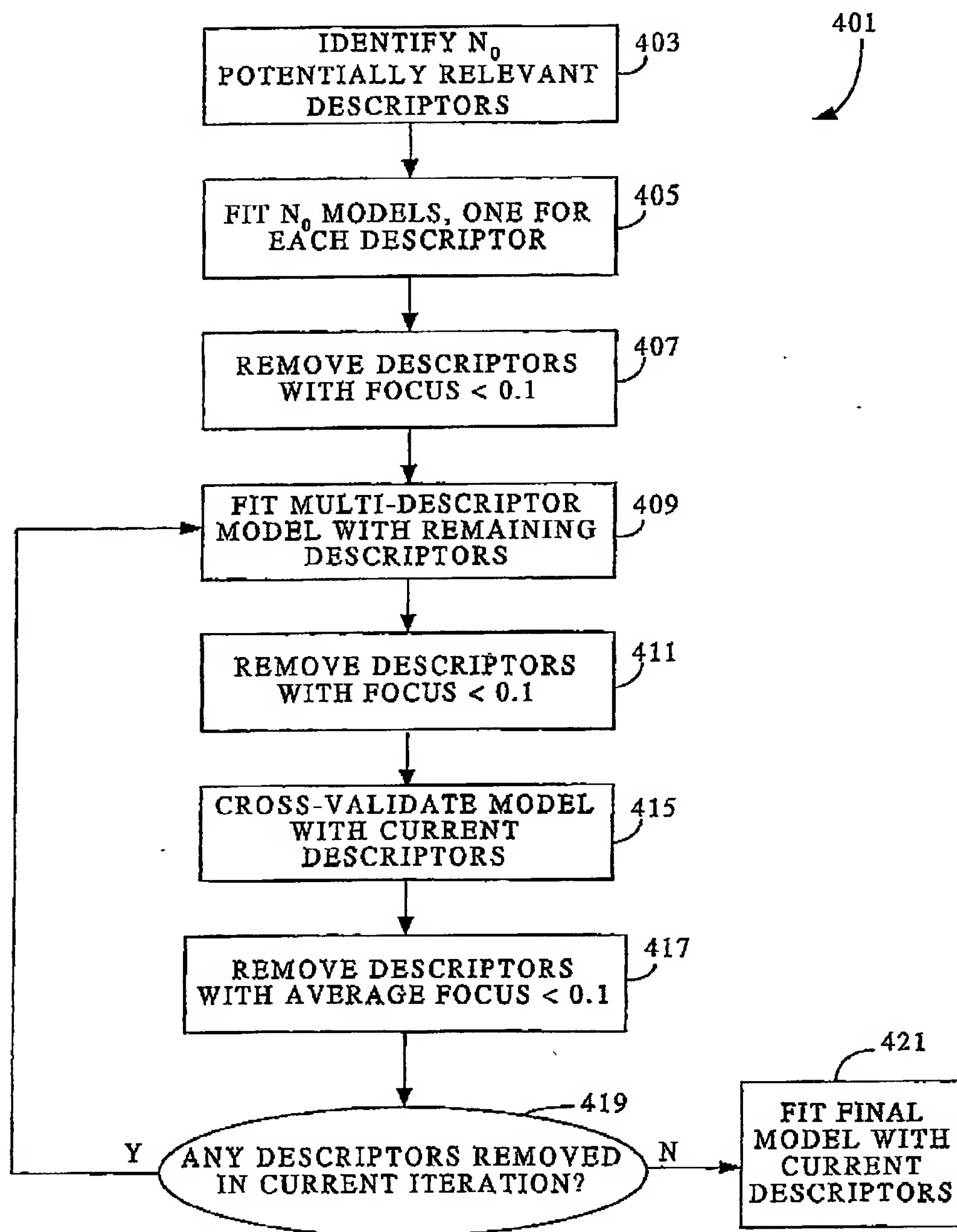


FIGURE 4H

Sigmoid Optimization Function

$$f(\mathbf{x}) = t + \frac{h}{1 + \sum_{k=1}^{N_t} e^{-n_k(x_k - c_k)}}$$

$$f_o = s_y \left(\frac{\sum_{i=1}^{N_y} u_i (f(\mathbf{x}_i) - y_i)^2}{\sigma_y^2 \sum_{i=1}^{N_y} u_i} \right)$$

Weighted Mean Squared Error

$$+ s_c \sum_{k=1}^{N_x} \frac{(c_k - c_{0k})^2}{\sigma_{x_k}^2}$$

Center Constraint

$$+ s_n \sum_{k=1}^{N_x} |n_k| \sigma_{x_k}$$

Focus Constraint

$$+ s_t \frac{(t - t_0)^2}{\sigma_y^2}$$

Tare Constraint

FIGURE 4I

Sigmoid Optimization Starting Values

$$\begin{aligned}
 t_0 &= \min(y) \\
 h_0 &= \max(y) - t_0 \\
 v_i &= \frac{(y_i - t_0)^2}{\sigma_y^2} \\
 v'_i &= \frac{(h_0 + t_0 - y_i)^2}{\sigma_y^2} \\
 c_{h,k} &= \frac{\sum_{i=1}^{N_{\text{inp}}} u_i v_i x_{k,i}}{\sum_{i=1}^{N_{\text{inp}}} u_i v_i} \\
 c_{l,k} &= \frac{\sum_{i=1}^{N_{\text{inp}}} u_i v'_i x_{k,i}}{\sum_{i=1}^{N_{\text{inp}}} u_i v'_i} \\
 c_{0,k} &= \frac{c_{h,k} + c_{l,k}}{2} \\
 w_{h,k} &= \frac{\sum_{i=1}^{N_{\text{inp}}} u_i v_i (x_{k,i} - c_{h,k})^2}{\sum_{i=1}^{N_{\text{inp}}} u_i v_i} \\
 w_{l,k} &= \frac{\sum_{i=1}^{N_{\text{inp}}} u_i v'_i (x_{k,i} - c_{l,k})^2}{\sum_{i=1}^{N_{\text{inp}}} u_i v'_i} \\
 n_{0,k} &= \frac{c_{h,k} - c_{l,k}}{w_{h,k} w_{l,k}}
 \end{aligned}$$

FIGURE 4J

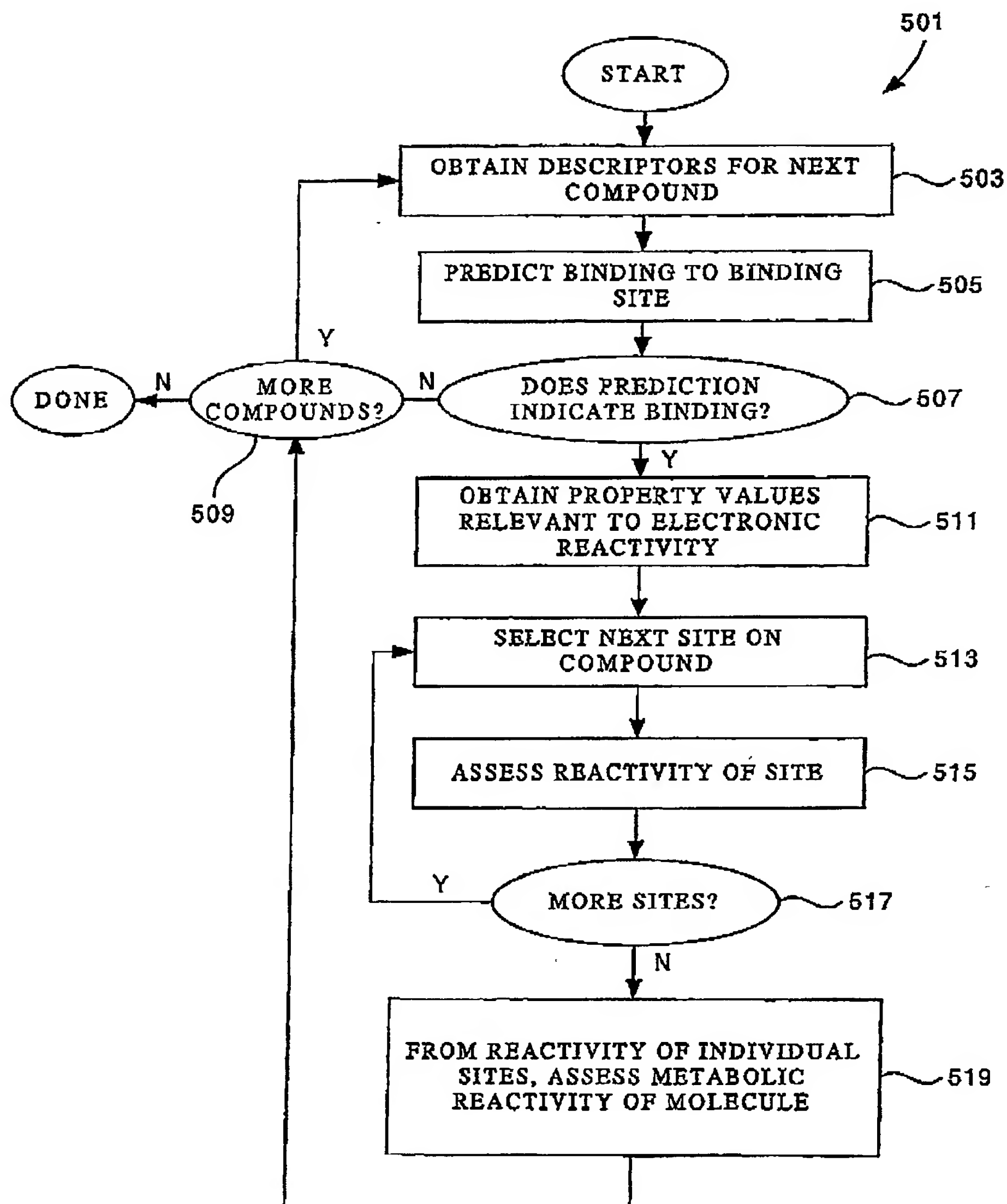


FIGURE 5

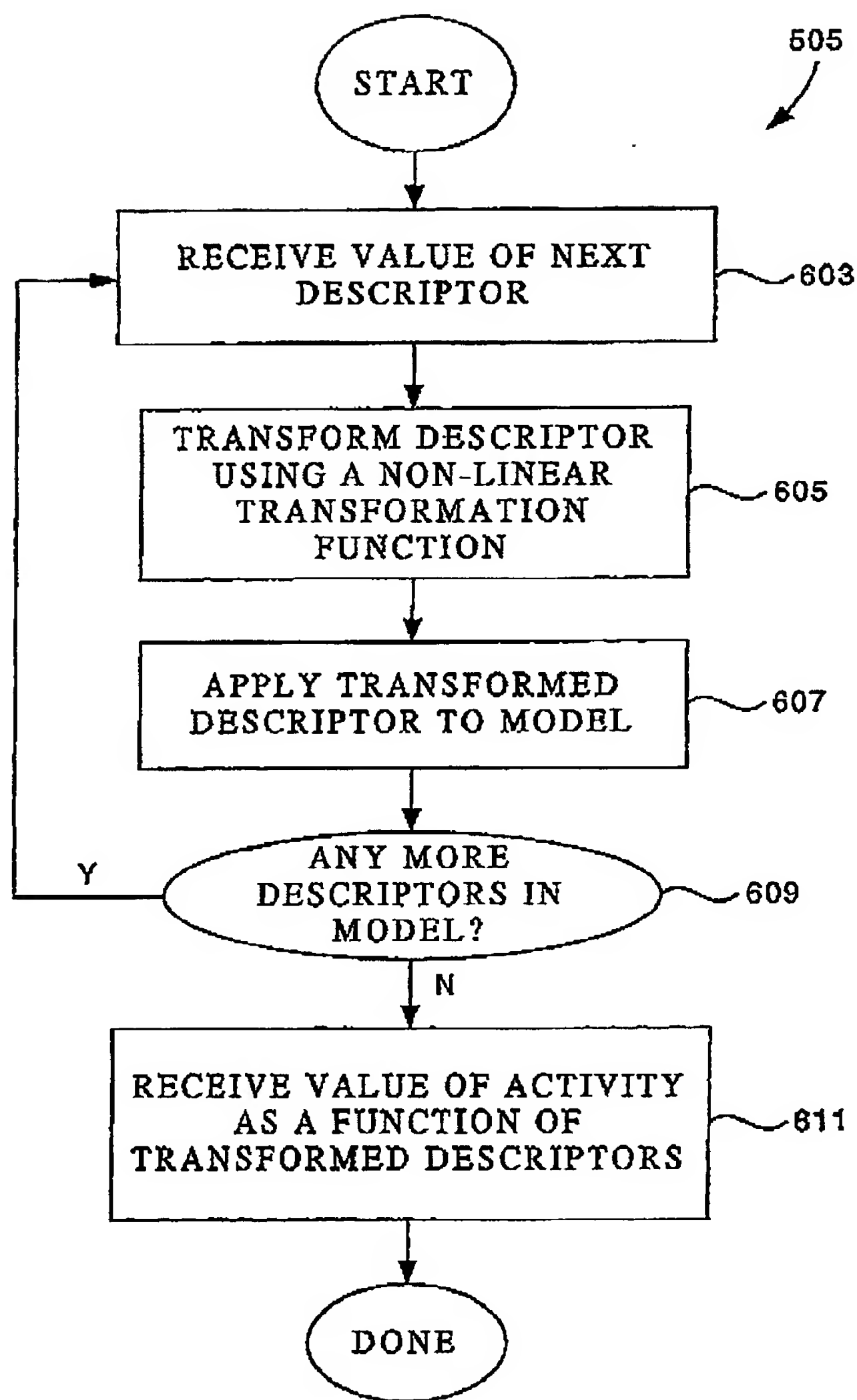


FIGURE 6

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Optimum logP

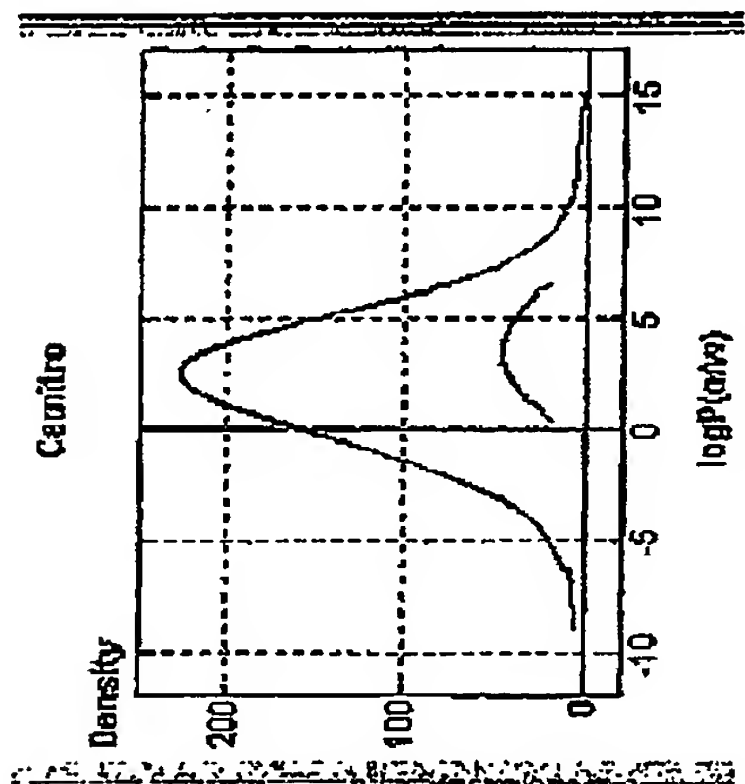
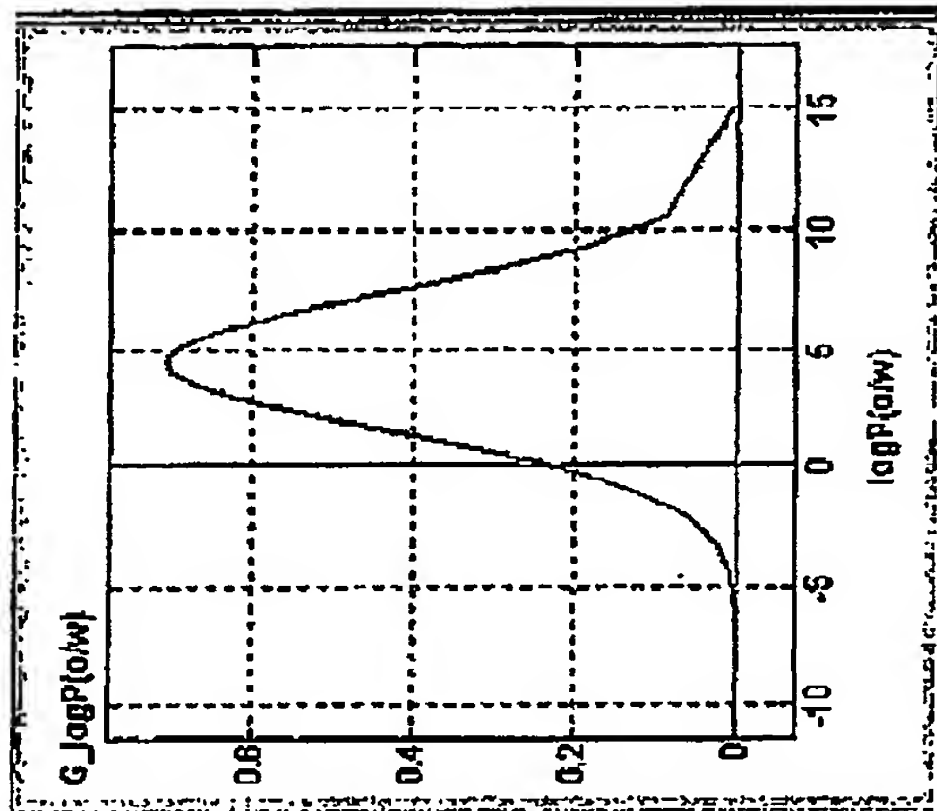


FIGURE 7A

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Optimum Formal Charge

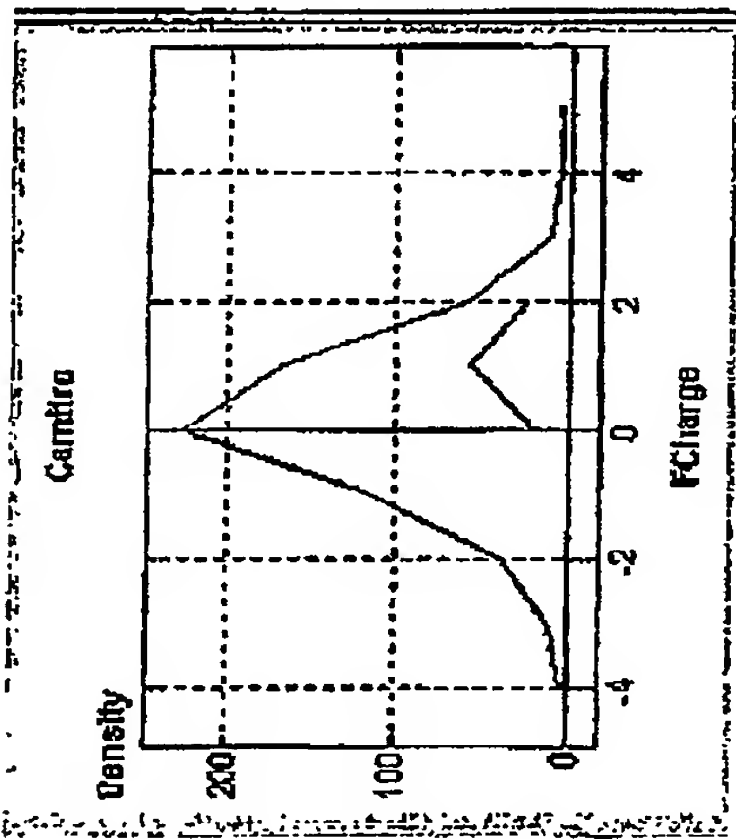
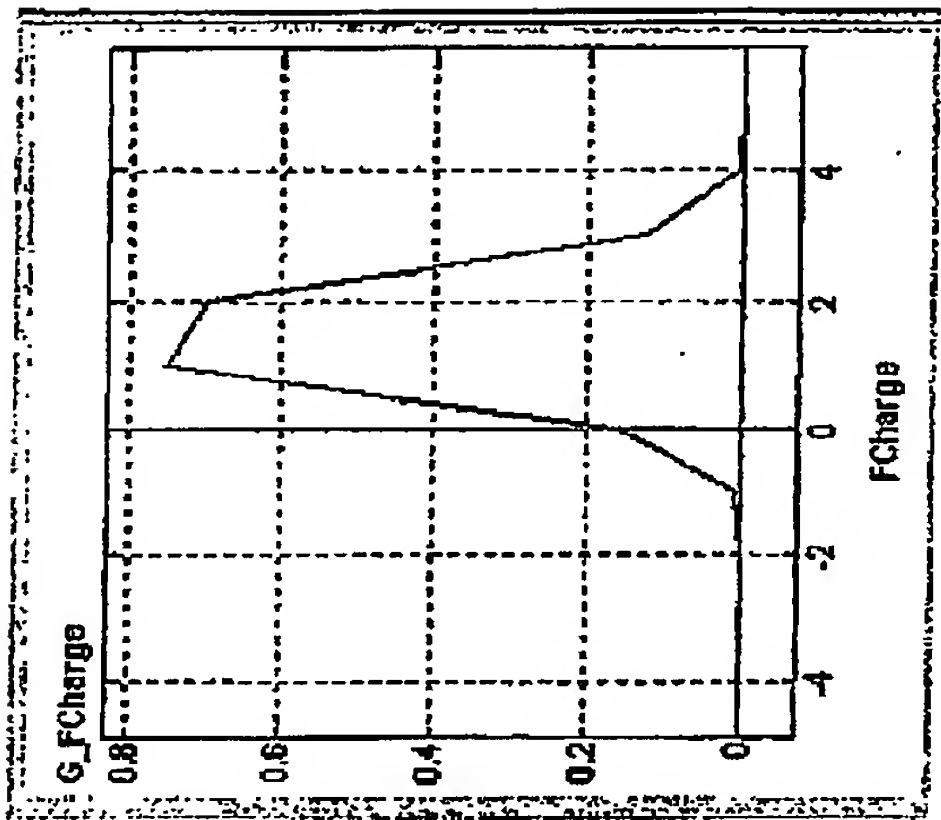


FIGURE 7B

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Automated Gaussian Fit

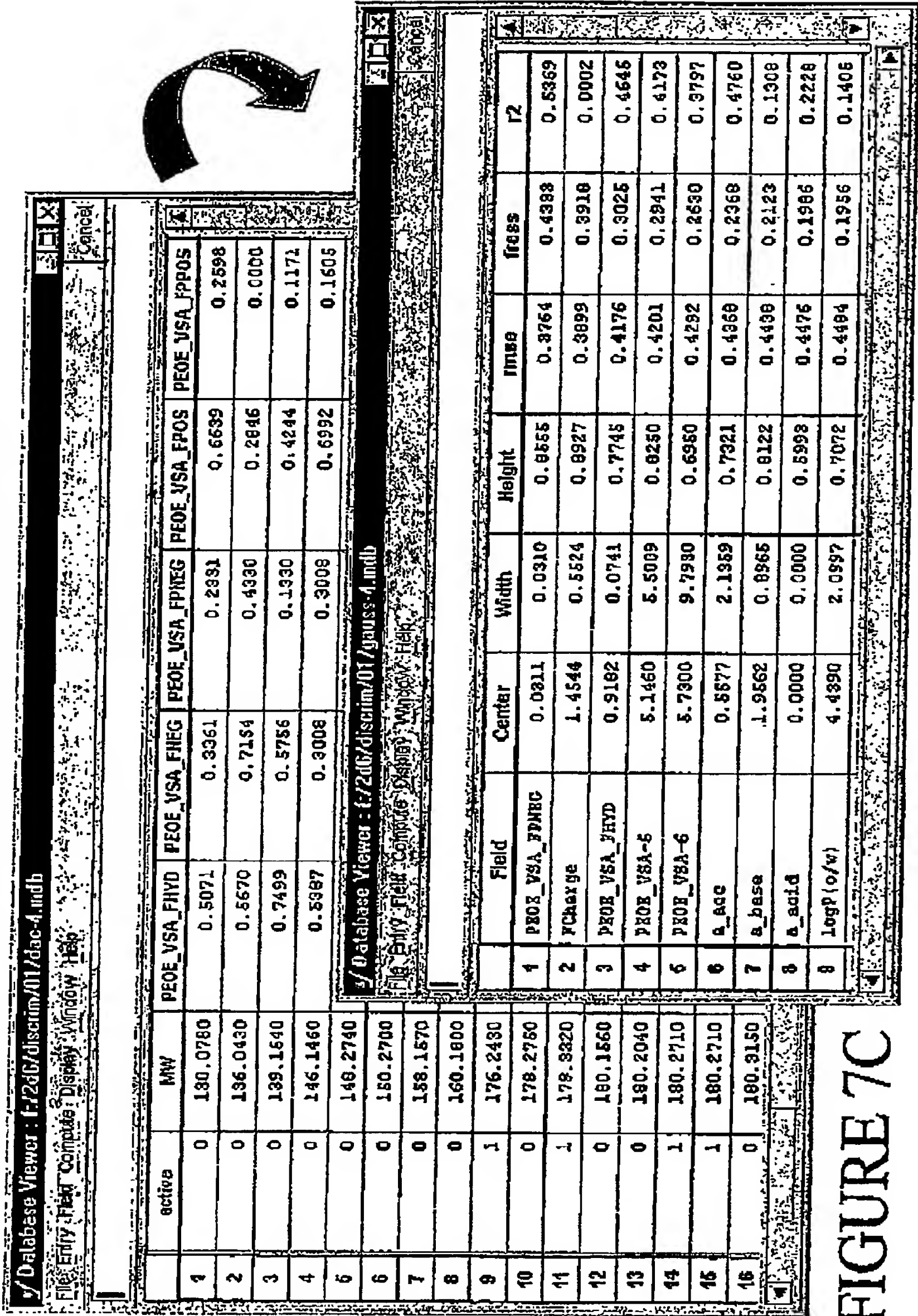


FIGURE 7C

2D6 K_i Model

Non-linear Size Relation

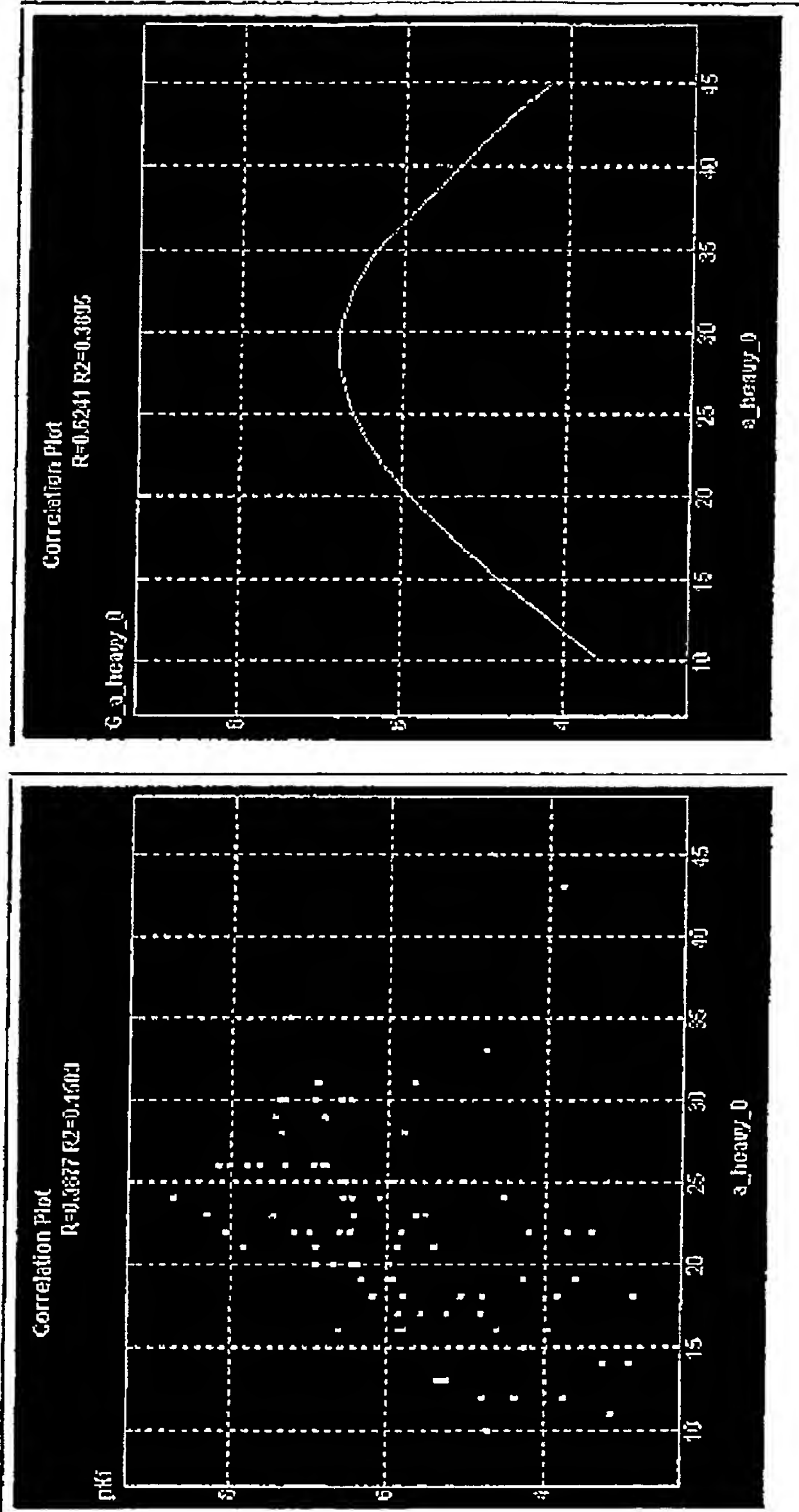


FIGURE 7D

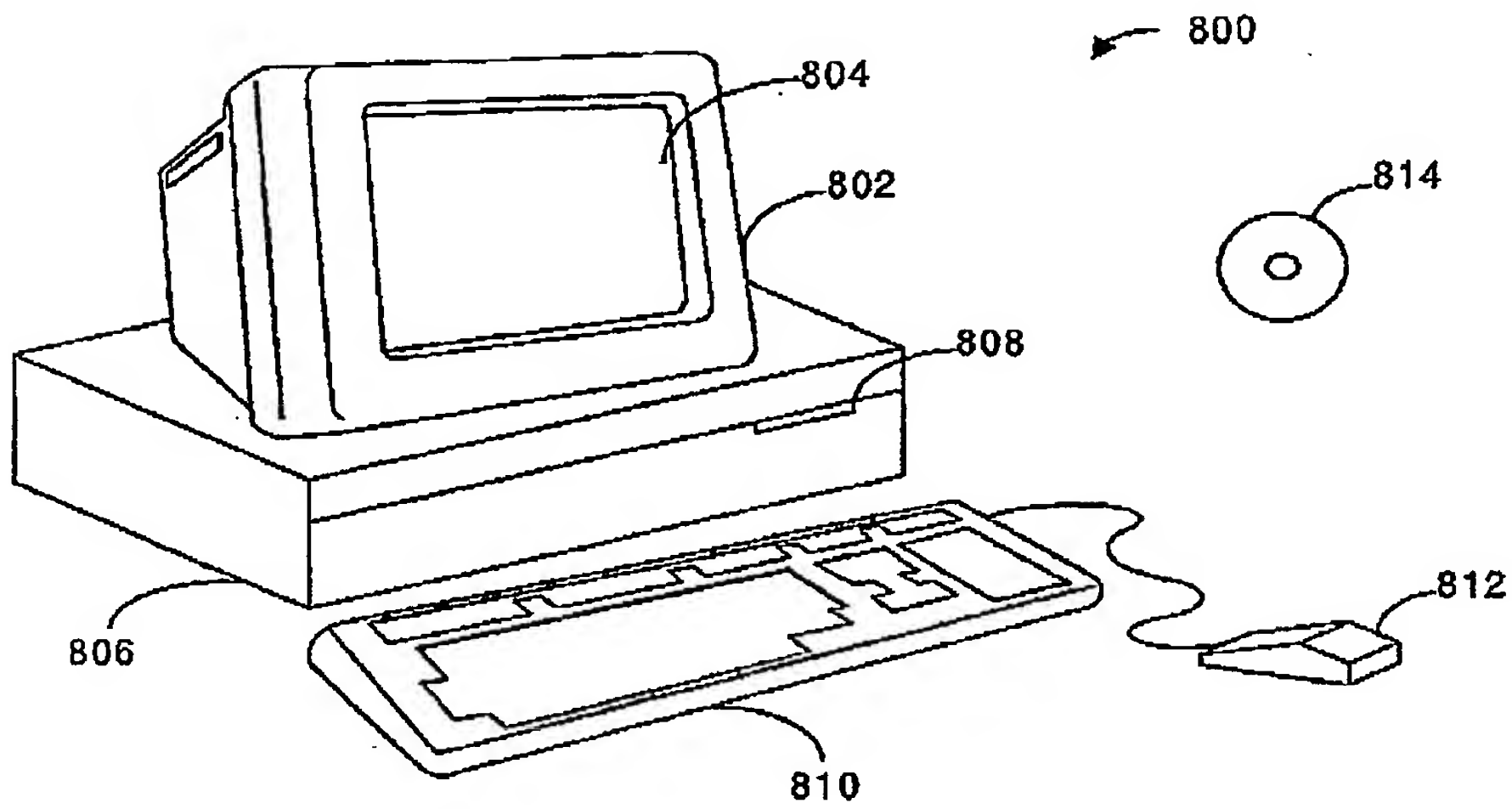


FIGURE 8A

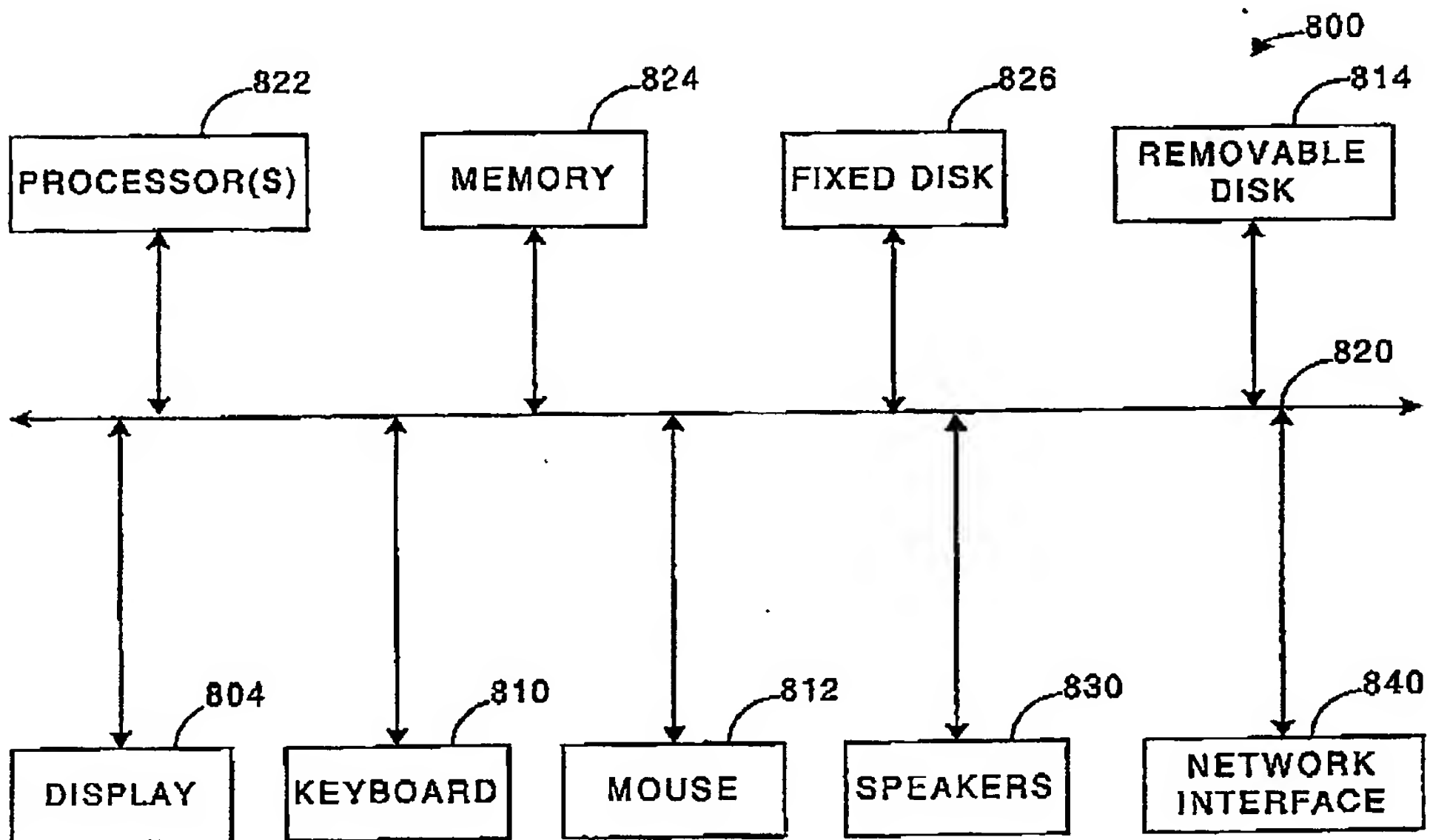


FIGURE 8B

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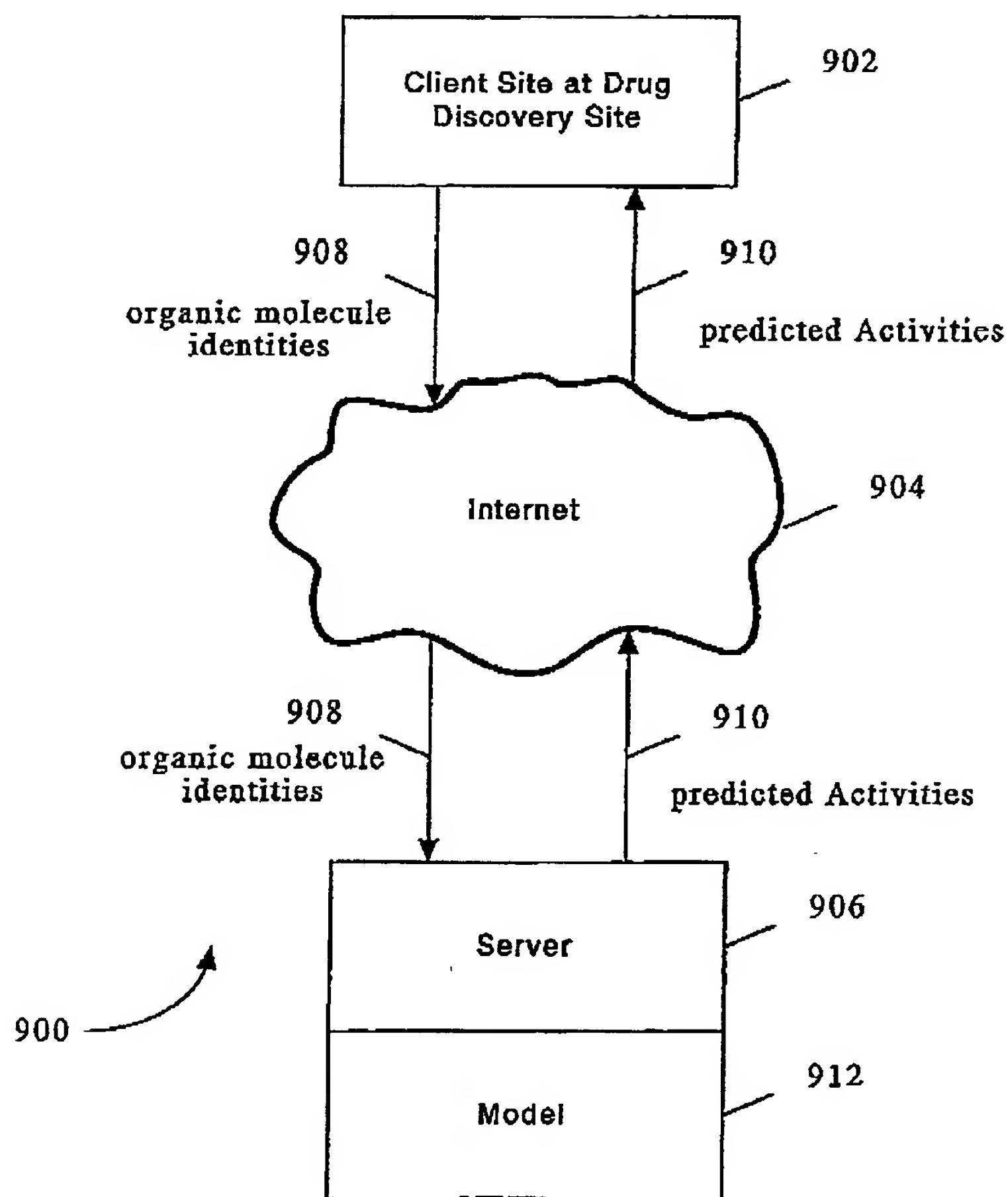


FIGURE 9

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